REMARKS

Applicants have added new claims 18-23. The new claims are supported throughout the specification, examples and figures.

Claim 18 is supported, for example, in the paragraph bridging pp. 18-19, and p. 45, lines 33-34. Claim 19 is supported, for example, at Figures 3A and 5. Claim 20 is supported, for example, at p. 43, lines 16-18, and Figures 3A-3D. Claims 21 and 23 are supported, for example, at page 28, lines 1-28. Claim 22 is supported, for example, at page 17, lines 3-31.

As such, these amendments do not constitute new matter, and their entry is respectfully requested.

Turning now to the specific rejections.

Claims 1, 4, 6 and 14-17 were rejected under 35 U.S.C. § 112, second paragraph. Examiner argues that the metes and bounds of the phrase "portion of at least two conserved regions" cited in the claim still cannot be determined.

Applicants respectfully disagree and submit that they are entitled to claim the modified gp120 in this manner, and that this rejection should be withdrawn for the following reasons.

The claims are directed to gp120 polypeptides, wherein at least two of the glycosylation sites proximal to the CD4 binding site or CCR5 or CXCR4 chemokine receptor binding site have been altered, and wherein the polypeptides maintain their native three-dimensional conformation.

This is a well known term. Indeed the structure of the lentivirus gp120 protein has been the subject of a great deal of inquiry, and both the primary and secondary structures of the gp120 primate lentivirus envelope protein have been established.

Primary structure i.e. the amino acid sequences of gp120: The amino acid alignment of gp120 between the different primate lentiviruses have shown that these proteins contain five variable (V1-V5) and five conserved (C1-C5) regions (page 3, lines 21-28 and references cited therein, and p. 42, lies 29-32, and the references cited therein). Indeed, the terms "conserved regions" mean that the amino acid residues are conserved across the various strains whereas those regions referred to as "variable" have substantial variability in amino acid residues among the strains. These sequence alignments can be easily performed and the finite number of possible amino acids involved in any particular conserved and/or variable region can be readily determined by the skilled artisan using sequence analysis, which is taught, for example in the paragraph bridging pages 19 and 20. Moreover, the discussion at page 28 and the examples provide substantial guidance. As explained at page 28, preferred deletions are directed to regions such as V1/V2 and C1 and C5 which are typically not part of the CD4 binding site.

As explained at page 18, to produce the visualized diffractable crystal the V1, V2, and V3 regions were deleted as well as portions of the C_1 and C_5 regions. Thus, the present specification and figures directly teach the skilled artisan about the secondary structure of gp120. See, for example, the discussion at pages 43-45 and the accompanying figures.

Combining the data readily available from the primary structural sequence alignment and the approximate positions of these sequences in the three-dimensional structure as taught in the specification and Figures of this application allows the skilled artisan to readily determine the finite number of possible combinations of amino acids and conserved regions and create a peptide that maintain the three-dimensional structure of the gp120 protein or parts of it. These amino acids form the metes and bounds of the "portion" as referred to in the phrase "portion of the at least two conserved regions" of the present claims.

Applicants give specific examples. For example, applicants teach specifically that the gp120 core is composed of inner domain, outer domain and a bridging antiparallel β sheet (p. 43, lines 16-18). Applicants further teach, for example, that the strands from the gp120 conserved C4 region and the conserved V1/V2 loop stem contribute the "bridging" antiparallel β-sheet (p. 44, lines 18-22, and Figure 3A). Applicants teach that a CD4 binding site is flanked by C3 residues 368-370, and C4 residues 427-457 (p. 28, lines 1-3). Applicants also teach how to replace the V1/V2 loop stem (p. 28, lines 26-28). Applicants further illustrate portions of C1 and C5 that were removed without affecting the overall conformation of the exposed immunogenic epitopes of the deglycosylated peptides (p. 28, lines 7-8) and specifically exemplify possible deletions (p. 41, lines 3-5).

Therefore, the variability in the number of possible amino acid residues is clearly limited to the residues taking part in the structures forming the three-dimensional structure. Thus, because the number of amino acid residues corresponding to the C1-C5 regions is finite, there are relatively few amino acid combinations to even test to determine the various possible combinations that are covered by the claims. Moreover, in light of the structural data illustrated in the Figures 1-5 of the application, the residues taking part in forming the overall three dimensional structure of a discontinuous conserved epitope of the wild-type gp120 protein or parts thereof are readily determinable. Applicants reiterate, that the functionally requirements put readily discernable limits on what regions must be present. This language has been accepted by the U.S. PTO in patents including those relied upon by the Examiner in the July 14, 2003 Office action. Therefore, Applicants submit that the rejection should be withdrawn.

Claim 6 was further rejected under 35 U.S.C. § 112, second paragraph. Examiner contended that the terms "a cavity", "a defined turn structure" and "interface" are not defined.

In view of the description of the specification, the Figures and the accompanying text, Applicants respectfully submit that there would be no ambiguity as to the terms "a cavity", "a defined turn structure" and "interface" as referred to in the claims. As discussed in the background of the application, substantial scientific interest has been directed to the HIV envelope protein since 1985 (see pages 2-3 of the present application). Further, the paragraph bridging pages 3 and 4 explains that gp120 protein compises conserved regions, and variable regions, disulfide bonds, loop-like structures, etc.

The present application, as discussed, provides, for example, in Figures 3A and 5, a ribbon drawing of the HIV gp120 glycoprotein representing its three-dimensional structure, and Figures 1, 2, and 3B-3D are surface diagrams of the three-dimensional structure of gp120. Figures 3B and 3C show the molecular surface of the gp120 indicating variability among primate immunodeficiency viruses. Figures 4A-D show the spatial relationship of epitopes on the HIV-1 gp120 glycoprotein. Finally, Figure 5 provides a schematic of the expected arrangement of the HIV-1 gp120 glycoprotein in a trimeric complex.

Accordingly, Applicants respectfully submit that in light of the Figures and the present specification the terms used in the claims would readily be understood.

For example, the Examiner questioned how to identify a "cavity." Applicants respectfully submit that by just looking at the Figures one can identify cavities. Applicants explicitly identify the cavity corresponding to the Phe residue at position 43 of the wild type HIV-1 HXBc2 strain (see, for example, paragraphs bridging pp. 18-19, and p. 45, lines 33-34).

With respect to introducing amino acid at a "defined turn structure," Applicants, again, point out that the skilled artisan knows that when one is talking about a three-dimensional structure the defined turn is the position in the protein chain where the chain turns back on itself. By looking at the Figures, one can readily identify such structures, e.g., the various loops V1/V2, V3, V4 (see, for example, Figure 3A and Figure 5). In addition, other turns that are readily identified in Figure 5 would be ∠D, ∠E etc. Thus, this term is well known to the skilled artisan as well as exemplified in the specification.

With respect to the term "interface", page 22, lines 29-33, specifically gives a citation to methods on how to increase the hydrophobicity across the domain interface to push the domains apart to better expose them to the immune system. The term "domain interface" naturally refers to the interface between the domains in the three-dimensional tertiary structure of the gp120 protein shown in Figures 1-5. Applicants further teach that the gp120 core is composed of inner domain, outer domain and a bridging antiparallel β sheet (p. 43, lines 16-18). The interfaces between these domains can be readily seen, for example, in Figures 3A-3D. Therefore, in light of the cited methods and the Figures, applicants submit that the term "interface" is adequately defined in the specification.

Applicants respectfully submit that the skilled artisan given the extensive teaching of the specification and the Examples described therein would have no difficulty with making and using the various embodiments claimed.

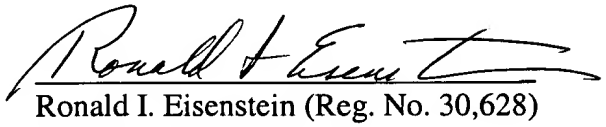
Accordingly, Applicants respectfully submit that this rejection of the claims should be withdrawn.

In view of the foregoing, Applicants respectfully submit that all claims are in condition for allowance. Early and favorable action is requested.

If any additional fee is required, please charge Deposit Account No. 50-0850.

Date: June 23, 2004

Respectfully submitted,



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